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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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JEFFREY M. GREENMAN
BAYER PHARMACEUTICALS CORPORATION
400 MORGAN LANE
WEST HAVEN, CT 06516

EXAMINER	
JOYCE, CATHERINE	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/675,406	EVELEIGH ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *6-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. Claims 1-15 are pending, claims 6-15 are withdrawn from consideration as being drawn to non-elected invention, and claims 1-5 are under examination.

2. Applicant's election of the invention of Group I and the species "cancer of the respiratory tract" and "blood" in the reply filed on July 14, 2006 is acknowledged. Because Applicant did not point out any errors in the restriction requirement, the election is treated as an election without traverse.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 3 and 4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single,

simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims, as drawn to the elected invention, are as follows:

A method to monitor the response of a patient being treated for cancer by administering a anti-cancer agent, comprising the steps of: (a) determining the level of expression of one or more one biomarker(s) in a first biological sample taken from the patient prior to treatment with the anti-cancer agent; (b) determining the level of expression of the biomarker in at least a second biological sample taken from the patient subsequent to the initial treatment with the anti-cancer agent; and (c) comparing the level of expression of the biomarker in the second biological sample with the level of expression of the biomarker in the first biological sample; wherein a change in the level of expression of the biomarker in the second biological sample compared to the level of expression of biomarker in the first biological sample indicates that the effectiveness of the treatment with the anti-cancer agent (claim 1),

wherein the anti-cancer agent is a Raf kinase inhibitor (claim 3),

wherein the biomarker is adrenomedullin (claim 4).

The specification teaches that mice were implanted with a human pancreatic carcinoma cell line (MiaPaCa) or a lung cancer cell line (WCI-H460) and were subsequently treated with a Raf kinase inhibitor after tumors became established in the mice (Example 1). The specification further teaches that an analysis of adrenomedullin RNA expression of tumor samples from the mice containing the MiaPaCA cell line at 1, 4, 7 and 24 hours after Raf kinase inhibitor treatment showed a decrease in

adrenomedullin RNA levels in cancers derived from the MiaPaCa cancer cell line (pages 35-36, Table 1, and Figures 1 and 2). The specification also teaches that a number of studies have suggested that inhibition of Raf kinase is an important target for cancer therapy (page 2). The specification also teaches that adrenomedullin is a secreted survival or growth factor that has been shown to by secreted by many human tumor types (page 2).

The teaching of specification cannot be extrapolated to enable the claims because one of skill in the art could not predict that the invention would function as claimed. In particular, the teaching in the specification is not sufficient to establish that a Raf kinase inhibitor would have an affect on adrenomedullin RNA levels in tumors in vivo because of the art recognized differences between tumor cells derived from a cell line and tumor cells in an in vivo tumor. For example, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body

has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, based on cell culture data it could not be predicted that, in the *in vivo* environment, the invention would function as claimed. Further, cancer treatment is known in the art to be unpredictable. In particular, Gura (1997, Science 278:1041-1042) teaches that researchers face the problem of sifting through potential anti-cancer agents to find ones promising enough to make human clinical trials worthwhile and teaches that, since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para.).

Thus, given the teaching in the art on the unpredictably of cancer treatment and the unpredictability of a correlation between cultured cells and cancer cells in vivo, and the lack of guidance in the specification on these issues such as by way of working examples, practice of the invention would require undue experimentation.

5. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, for lack of written description

The claim is drawn to a method to monitor the response of a patient being treated for cancer by administering a anti-cancer agent, comprising the steps of: (a) determining the level of expression of one or more one biomarker(s) in a first biological sample taken from the patient prior to treatment with the anti-cancer agent; (b) determining the level of expression of the biomarker in at least a second biological sample taken from the patient subsequent to the initial treatment with the anti-cancer agent; and (c) comparing the level of expression of the biomarker in the second biological sample with the level of expression of the biomarker in the first biological sample; wherein a change in the level of expression of the biomarker in the second biological sample compared to the level of expression of biomarker in the first biological

sample indicates that the effectiveness of the treatment with the anti-cancer agent, wherein the anti-cancer agent is a Raf kinase inhibitor.

Although drawn to the DNA arts, the finding in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. at 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Although the inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of "a Raf kinase inhibitor" per Lilly by structurally describing a representative number of species of "a Raf kinase inhibitor" or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe "a Raf kinase inhibitor" in the claimed method in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any Raf kinase inhibitors, nor does the specification provide any partial structure of such Raf kinase inhibitors, nor any physical or chemical characteristics of Raf kinase inhibitors, nor any functional characteristics coupled with a known or disclosed correlation between structure and

function, other than the description of the Raf kinase inhibitor, ISIS 5132, a phosphorothioate antisense oligonucleotide. Although the specification discloses a single "Raf kinase inhibitor", this does not provide a description of "a Raf kinase inhibitor" of the claimed methods that would satisfy the standard set out in Enzo.

The specification also fails to describe the claimed "a Raf kinase inhibitor" by the test set out in Lilly. The specification describes only the Raf kinase inhibitor ISIS 5132, a phosphorothioate antisense oligonucleotide. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of "a Raf kinase inhibitor" and therefore, does not provide an adequate written description of the claimed method that employs "a Raf kinase inhibitor".

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-2 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Ebert et al. (1997, Anticancer Research 17(4B):2875-8) (abstract only).

The claims, as drawn to the elected invention, are as follows:

A method to monitor the response of a patient being treated for cancer by administering a anti-cancer agent, comprising the steps of: (a) determining the level of

expression of one or more one biomarker(s) in a first biological sample taken from the patient prior to treatment with the anti-cancer agent; (b) determining the level of expression of the biomarker in at least a second biological sample taken from the patient subsequent to the initial treatment with the anti-cancer agent; and (c) comparing the level of expression of the biomarker in the second biological sample with the level of expression of the biomarker in the first biological sample; wherein a change in the level of expression of the biomarker in the second biological sample compared to the level of expression of biomarker in the first biological sample indicates that the effectiveness of the treatment with the anti-cancer agent (claim 1),

wherein the cancer is cancer of respiratory tract (claim 2),

wherein said biological sample is a blood sample (claim 5).

Ebert et al. teaches that during the monitoring of response to chemo-/radiotherapy in non-small cell lung carcinoma the changes in marker levels of CYFRA 21-1 were compared to the clinical assessment according to the standard criteria of WHO, and that concordant results were obtained for CYFRA 21-1 with progressive disease most effectively indicated by CYFRA 21-1 levels.

8. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Catherine Joyce
Examiner
Art Unit 1642